Pharmacy Update
March/April 2003

Drug Information Service
Department of Pharmacy
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196
www.cc.nih.gov/phar

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor
Karim Anton Calis, Pharm.D., M.P.H.
Clinical Specialist, Endocrinology & Women's Health, and Coordinator, Drug Information Service
kcalis@nih.gov

In This Issue

- Ezetimibe (Zetia™): A Brief Review
- Selected FDA Safety Alerts
- Formulary Update
- Drug Information Service

Ezetimibe (Zetia™): A Brief Review

Ezetimibe is a new, oral antihyperlipidemic agent that was recently approved for use in the United States. This drug is indicated for use alone or in combination with HMG-CoA reductase inhibitors as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL cholesterol, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia. Ezetimibe is also indicated in combination with atorvastatin or simvastatin for the reduction of elevated total cholesterol and LDL cholesterol in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid lowering therapies (e.g., LDL apheresis) or if such treatments are not available. Ezetimibe is also indicated as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.[1]

Clinical Pharmacology

Ezetimibe is an orally active inhibitor of the absorption of dietary and biliary cholesterol and related phytosterols. Structurally it is a 2-azetidinone.[1,2] Ezetimibe inhibits the transport of cholesterol across the intestinal wall. It appears to have activity at a membrane protein in the brush border membrane of small intestinal enterocytes.[3]

In a placebo-controlled crossover study, ezetimibe reduced cholesterol absorption 54%, from 50% on placebo to 23% on ezetimibe ($P<0.001$). Cholesterol synthesis increased 89% and the ratio of lathosterol-to-cholesterol, an indirect marker of cholesterol synthesis, increased 72% ($P<0.001$) during ezetimibe therapy. Bile acid synthesis was increased slightly (308 mg/d vs 264 mg/d). LDL was reduced 20.4% and total cholesterol was reduced 15.1%; the absolute benefit reduction between the two treatment groups was -13.2% for the total cholesterol and -22.3% for the LDL cholesterol. The levels of the noncholesterol sterols campesterol and sitosterol were reduced 48% and 41%, respectively.[4] In humans, ezetimibe reduces LDL-cholesterol, total cholesterol, Apo B, and triglycerides, and increases HDL in patients with hypercholesterolemia.[1,5-8] In two large, double-blind, placebo-controlled studies LDL reduction was similar in groups with the lowest and highest quartiles of cholesterol and fat intake, suggesting ezetimibe maintains activity in patients with varying degrees of compliance with an NCEP Step 1 or stricter diet.[9]

It has cholesterol lowering activity in several animal models, including cholesterol-fed hamsters and cholesterol-fed rhesus monkeys.[2,10,11] In animals fed a high-fat diet, ezetimibe did not affect body weight, insulin, or leptin, but normalized cholesterol and triglyceride levels.[11] Ezetimibe can also inhibit the progression of atherosclerotic lesions.[12] Cholesterol lowering has been modest, as most animals compensate for the loss of biliary cholesterol by increasing hepatic cholesterol synthesis. This has prompted studies of the combined use of cholesterol absorption inhibitors and HMG-CoA reductase inhibitors. Ezetimibe has demonstrated synergistic cholesterol lowering activity administered in conjunction with lovastatin, pravastatin, fluvastatin, simvastatin, and atorvastatin.[13]

In animal models, ezetimibe did not affect the absorption of triglycerides, ethinyl estradiol, progesterone, vitamins A and D, and taurocholic acid.[10] In human studies ezetimibe had no effect on plasma concentrations of fat soluble vitamins A, D, and E, or adrenocortical steroid hormone production.[1]

Pharmacokinetics

Peak concentrations of ezetimibe occur within 4 to 12 hours after oral administration.[1] Ezetimibe is metabolized in the small intestine and liver via glucuronide conjugation, then undergoes biliary and renal excretion. The metabolite is excreted in the bile and returns to the site of action via enterohepatic recirculation.[1,14-16] Overall, 17% to 20% of the total amount absorbed is recycled into the central compartment via enterohepatic recirculation.[17] The glucuronide metabolite is more active than ezetimibe.[14] Ezetimibe accounts for 10% to 20% of the total drug in plasma, while the ezetimibe glucuronide accounts for 80% to 90% of the total drug in plasma.[1] Peak concentration of the glucuronide metabolite occurs 2 to 3 hours after administration.[15] Administration of ezetimibe with food does not affect total exposure to ezetimibe or ezetimibe plus the metabolite.[18] Ezetimibe and the ezetimibe glucuronide metabolite are highly plasma protein bound (greater than 90%).[1]

The ezetimibe and ezetimibe glucuronide terminal elimination half-lives are both approximately 22 hours.[1] Ezetimibe has no effect on the CYP450 enzymes 1A2, 2C8/9, 2D6, 3A4, or N-acetyltransferase.[1,19]

The pharmacokinetics of ezetimibe 10 mg once daily for 7 days have been evaluated in an open-label study enrolling 18 healthy adolescents 10 to 18 years of age. Pharmacokinetics were similar to those observed in adults, with a time to peak of 1 to 2 hours, extensive glucuronidation with enterohepatic recirculation, and a terminal elimination half-life of 20 to 29 hours.[20] In patients 65 years of age or older, plasma concentrations of total ezetimibe were approximately 2-fold higher than in younger subjects.[1]

Total ezetimibe area under the curve (AUC) was increased 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 to 6). In patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score 10 to 15) hepatic impairment, the mean AUC for total ezetimibe and ezetimibe were increased 3- to 4-fold and 5- to 6-fold, respectively. As the effects of exposure to these levels of ezetimibe are not known, ezetimibe use is not recommended in patients with moderate to severe hepatic impairment.[1] In patients with severe chronic renal failure, exposure to total ezetimibe and conjugated ezetimibe is increased about 50%; however, this increase is not expected to be clinically important.[21]

Comparative Efficacy

Primary Hypercholesterolemia – Monotherapy

Pooled results of two placebo-controlled, double-blind, 12-week studies enrolling a total of 432 patients were reported. In both studies ezetimibe or placebo was administered after a washout of lipid-altering agents and a 6-week placebo lead-in period. During the washout period, patients were stabilized on a National Cholesterol Education Program Step I diet. Enrolled patients had baseline plasma LDL-cholesterol levels greater than or equal to 130 and less than or equal to 250 mg/dL and plasma triglyceride levels less than or equal to 300 mg/dL. These studies enrolled a relatively healthy population; exclusion criteria included homozygous familiar hypercholesterolemia or non-type II hypercholesterolemia; body mass index greater than 35 kg/m^2; congestive heart failure (NYHA class III or IV); blood pressure greater than 160/95 mm Hg with or without therapy; cardiac dysrhythmias requiring medication; myocardial infarction, coronary artery bypass surgery, or angioplasty within 6 months of study entry; history of unstable or severe peripheral artery disease; active, severe unstable angina pectoris; fasting glucose level greater than 126 mg/dL; disorders of the hematologic, digestive, or central nervous system that would limit study participation or evaluation; diabetes mellitus requiring medical therapy; unstable endocrine disease; significant muscular disorder or disabling neuropathy; known impairment of renal function; active or chronic hepatic or hepatobiliary disease; treatment with psyllium or other fiber-based laxatives unless the regimen had been stable for greater than 4 weeks before the initial qualifying lipid determination; consumption of greater than 10 alcohol beverages per week; and use of oral corticosteroids, anticoagulants, quinidine, theophylline, barbiturates, antacids with aluminum, or and immunosuppressants. Nearly half of the enrolled patients (43%) were cigarette smokers. In study A, enrolling 243 patients (139 men, 104 women; 28 to 75 years of age), patients received placebo or ezetimibe 0.25, 1, 5, or 10 mg once daily before the morning meal. In study B, enrolling 189 patients (89 men, 100 women; 22 to 75 years of age), patients received placebo or ezetimibe 5 or 10 mg once daily before the morn-ing meal or at bedtime. In study A, LDL concentrations were reduced by 9.9% to 18.7% compared to placebo over the range of ezetimibe doses. All four doses were more effective than placebo ($P<0.01$). Apo B and total cholesterol were also reduced with all four ezetimibe doses compared with placebo. The maximal reduction in LDL-C (65% to 80%) was observed within 1 week, with the maximum effect occurring by the end of the second week of therapy. No effect on HDL-C, HDL-C subfractions, apo A-I, triglycerides, or lipoprotein(a) was observed. In study B, regimens of ezetimibe administered as either 5 or 10 mg in the morning or at night were all more effective than placebo. Mean LDL-C was reduced by 13.8% to 18.2% compared with placebo ($P<0.01$). The time of administration had no effect on response. The peak response was also observed within 2 weeks. Apo B and total cholesterol were also reduced compared with placebo ($P<0.01$). HDL-C was increased with each ezetimibe regimen compared to placebo ($P<0.05$), but no changes in HDL-C subfractions, apo A-I, triglycerides, or lipoprotein(a) were observed. In the pooled analysis, a 15% or greater reduction in LDL-C was observed in 54% of patients (67 of 124) treated with ezetimibe 5 mg and 67.8% of patients (80 of 118) treated with ezetimibe 10 mg, compared with 6.9% of placebo-treated patients (6 of 87). A 25% or greater reduction in LDL-C was observed in 15.3% of patients (19 of 124) treated with ezetimibe 5 mg and 22% of patients (26 of 118) treated with ezetimibe 10 mg, compared with 1.1% of placebo-treated patients (1 of 87).[5]

In a similar placebo-controlled, double-blind study enrolling 827 patients with primary hypercholesterolemia, ezetimibe was shown to be better than placebo. Following dietary stabilization on an NCEP Step I or stricter diet, a 2- to 12-week washout period, and a 4- to 8-week placebo run-in period, patients with a baseline LDL-C greater than or equal to 130 mg/dL and less than or equal to 250 mg/dL and triglycerides less than or equal to 350 mg/dL were randomized to received either ezetimibe 10 mg or placebo once daily each morning for 12 weeks. LDL-C was reduced by a mean of 17.7% in the ezetimibe-treated patients, compared to an increase of 0.8% in the placebo-treated patients (P<0.01). Reductions in LDL-C were observed by week-2 and maintained throughout the duration of the study. Subgroup analysis found consistent results regardless of risk-factors, gender, age, race, and baseline lipid profile. Triglycerides were reduced 7% in the ezetimibe group compared with a 1% reduction in the placebo group. HDL cholesterol was reduced 1% in the placebo group and increased 1% in the ezetimibe group.[1,22]

Comparable results were obtained in another similar placebo-controlled, double-blind study enrolling 892 patients with primary hypercholesterolemia. Following at least 2 weeks on an NCEP Step I or stricter diet and a 4- to 8-week placebo run-in, patients with LDL-C greater than or equal to 130 mg/dL and less than or equal to 250 mg/dL and triglycerides less than or equal to 350 mg/dL were treated with ezetimibe 10 mg or placebo once daily in the morning for 12 weeks. Direct LDL-C was unchanged in the placebo group (0.4%) and reduced by a mean of 16.9% in the ezetimibe group (P<0.01). Apolipoprotein B was reduced 1.4% in the placebo group and 15.5% in the ezetimibe group (P<0.01). HDL-C was reduced 1.6% in the placebo group, but increased 1.3% in the ezetimibe group (P<0.01). Triglycerides were increased 5.7% in the placebo group and reduced by 5.7% in the ezetimibe group (P<0.01). The reduction in LDL-C occurred within the first 2 weeks and was maintained for the duration of the study.[6,23]

The results observed in these studies are consistent with those previously observed in a Phase II dose-finding study evaluating ezetimibe at doses ranging from 1 to 40 mg once daily. One hundred and twenty-four patients with LDL-C between 130 mg/dL and 250 mg/dL and triglyceride levels less than 300 mg/dL were enrolled. Patients were treated with placebo, ezetimibe 1 mg, 5 mg, 10 mg, 20 mg, or 40 mg, or lovastatin 40 mg once daily for 8 weeks. All ezetimibe doses reduced LDL-C compared with placebo (P<0.05). LDL-C increased 3.8% in the placebo group, but was reduced by 14.6% in the ezetimibe 1 mg group, 15.7% in the 5 mg group, 16.4% in the 10 mg group, 17.9% in the 20 mg group, 20% in the ezetimibe 40 mg group, and 31.8% in the lovastatin 40 mg group.[24]

Primary Hypercholesterolemia – Combination Therapy with an HMG-CoA Reductase Inhibitor

Several studies also evaluated ezetimibe in conjunction with HMG-CoA reductase inhibitors. The efficacy of ezetimibe added to ongoing statin therapy was assessed in a double-blind, placebo-controlled study enrolling 769 adults with primary hypercholesterolemia who had not achieved NCEP Adult Treatment Panel II goals with diet and statin monotherapy. Patients receiving a stable dose of statin for at least 6 weeks were randomized to receive concurrent placebo (390 patients) or ezetimibe 10 mg once daily (379 patients) for 8 weeks. Concurrent statin regimens included simvastatin 10 to 80 mg, atorvastatin 10 to 80 mg, lovastatin 10 to 40 mg, pravastatin 10 to 40 mg, fluvastatin 20 to 80 mg, and cerivastatin 0.2 to 0.8 mg. The mean change in LDL cholesterol from baseline (on statin therapy) was -25.1% with ezetimibe plus statin compared with -3.7% with placebo plus statin (P<0.001). HDL cholesterol increased 2.7% in the ezetimibe group and 1% in the placebo group (P<0.05). Triglycerides declined 14% in the ezetimibe group and 2.9% in the placebo group (P<0.001). NCEP LDL cholesterol treatment goals were reached in 71.5% receiving ezetimibe plus statin compared with 18.9% receiving placebo plus statin (P<0.001). Results were generally consistent across the group of statins and across patient types (gender; age less than or greater than 65 years; Caucasian or non-Caucasian; NCEP category I, II, or III; body mass index).[25,26]

Pooled results from four double-blind, placebo-controlled studies evaluating ezetimibe in conjunction with statin therapy were also reported. Patients were all stabilized on an NCEP Step I or stricter diet. After a 2- to 12-week washout period and a 4-week single-blind placebo run-in period, patients with LDL-C 145 to 250 mg/dL and triglycerides less than 350 mg/dL were randomized to 12 weeks of therapy with ezetimibe 10 mg, statin monotherapy, ezetimibe 10 mg plus a statin, or placebo. The mean change in LDL cholesterol from baseline was -44% in the atorvastatin group (10 to 80 mg, 248 patients) compared to -56% in the ezetimibe 10 mg plus atorvastatin group (10 to 80 mg, 255 patients, P<0.01); -37% in the simvastatin group (10 to 80 mg, 263 patients) compared to -51% in the ezetimibe 10 mg plus simvastatin group (10 to 80 mg, 274 patients, P<0.01); -25% in the pravastatin group (10 to 40 mg, 205 patients) compared to -39% in the ezetimibe 10 mg plus pravastatin group (10 to 40 mg, 204 patients, P<0.01); and -25% in the lovastatin group (10 to 40 mg, 220 patients) compared to -40% in the ezetimibe 10 mg plus lovastatin group (10 to 40 mg, 192 patients, P<0.01).[27]

The simvastatin study enrolled a total of 668 patients, 70 treated with placebo, 61 with ezetimibe alone, 263 with simvastatin alone (10 to 80 mg/day), and 274 with ezetimibe plus simvastatin. Direct LDL was reduced by 1.3% in the placebo group, 18.1% in the ezetimibe group, 36.1% in the simvastatin group, and 49.9% in the ezetimibe plus simvastatin group (P<0.03 for ezetimibe plus simvastatin vs simvastatin alone). HDL cholesterol was increased by 0.9% in the placebo group, 5.1% in the ezetimibe group, 6.9% in the simvastatin group, and 9.3% in the ezetimibe plus simvastatin group (P<0.03 for ezetimibe plus simvastatin vs simvastatin alone). Triglycerides increased 2.4% in the placebo group, and declined by 8.3% in the ezetimibe group, 16.6% in the simvastatin group, and 24.1% in the ezetimibe plus simvastatin group (P≤0.03 vs simvastatin alone).[28]

Similar results were observed in the atorvastatin study which enrolled a total of 628 patients. Direct LDL was increased 5.9% in the placebo group and reduced by 18.4% in the ezetimibe group, 42.4% in the atorvastatin group, and 54.5% in the ezetimibe plus atorvastatin group (P<0.01 vs atorvastatin alone). HDL cholesterol was increased 3.7% in the placebo group, 4.2% in the ezetimibe group, 4.3% in the atorvastatin group, and 7.3% in the ezetimibe plus atorvastatin group (P<0.01 vs atorvastatin alone). Triglycerides were increased 4.4% in the placebo group, and declined by 3.4% in the ezetimibe group, 21.5% in the atorvastatin group, and 29.5% in the ezetimibe plus atorvastatin group (P<0.01 vs atorvastatin alone).[29] For each statin and at each statin dose, administration in conjunction with ezetimibe produced greater reductions in LDL cholesterol and triglyceride levels than those observed with the statin alone.[1]

Ezetimibe was evaluated in conjunction with atorvastatin in an evaluator-blinded, placebo-controlled study enrolling 32 patients with hypercholesterolemia (LDL-C ≥130 mg/dL) stabilized on an NCEP Step I diet. Patients received atorvastatin 10 mg, ezetimibe 10 mg, atorvastatin 10 mg plus ezetimibe 10 mg, or placebo once daily in the morning for 14 days. On day-14, LDL-C was reduced by a mean of 6.9% in the placebo group, 22.7% in the ezetimibe monotherapy group, 40% in the atorvastatin monotherapy group, and 55.7% in the combination group (P≤0.02 vs placebo). Total cholesterol was reduced by 6.1%, 15.4%, 28.4%, and 38%, respectively. HDL-C was reduced 12.8% in the placebo group and 11.3% in the ezetimibe monotherapy group, but by only 0.5% in the atorvastatin group and 1.1% in the combination group. Triglycerides were increased in the placebo (22.6%) and ezetimibe monotherapy group (32.8%), but were unchanged in the atorvastatin group (0.5%) and declined in the combination group (-8.6%).[7]

Ezetimibe was also evaluated in conjunction with simvastatin in an evaluator-blinded, placebo-controlled study enrolling 58 patients with hypercholesterolemia (LDL-C ≥130 mg/dL) stabilized on an NCEP Step I diet. Patients received placebo, simvastatin 10 mg, or simvastatin plus ezetimibe 0.25 mg, 1 mg, or 10 mg, once daily in the morning for 14 days. At the 10 mg ezetimibe dose, an additional 17% reduction in LDL-C was observed (-51.9%) beyond that observed with simvastatin alone (-34.9%; P<0.01). A 50% reduction in LDL-C was observed in 75% of patients treated with the combination of simvastatin 10 mg plus ezetimibe 10 mg.[24,30] In another study enrolling 24 patients with hypercholesterolemia, ezetimibe 10 mg plus simvastatin 20 mg reduced LDL-C an additional 18% beyond that observed with simvastatin 20 mg alone.[24,30] Additional reductions of 16% to 18% have been reported with ezetimibe 5, 10, and 20 mg when administered in conjunction with lovastatin 20 mg.[24]

Ezetimibe was evaluated in conjunction with cerivastatin in an evaluator-blinded, placebo-controlled study enrolling 32 patients with hypercholesterolemia (LDL-C ≥130 mg/dL) stabilized on an NCEP Step I diet. Patients received cerivastatin 0.3 mg, ezetimibe 10 mg, cerivastatin 0.3 mg plus ezetimibe 10 mg, or placebo once daily in the morning for 14 days. On day-14, LDL-C was reduced by a mean of 19.8% in the ezetimibe monotherapy group, 14.7% in the cerivastatin monotherapy group, and 33.3% in the combination group (P≤0.02 vs placebo and cerivastatin monotherapy), compared to an increase of 7.8% in the placebo group. Changes in the total cholesterol were a reduction of 11.8% with ezetimibe, 9.1% with cerivastatin, 23% with cerivastatin plus ezetimibe, and an increase of 6% with placebo. HDL-C declined slightly in the placebo (1.5%) and ezetimibe groups (4%), but was increased slightly in the cerivastatin (2.1%) and combination groups (4.1%). The triglyceride levels increased by 29.2%, 4.6%, 0.6%, and 3.2%, respectively.[8]

Homozygous Familial Hypercholesterolemia

The addition of ezetimibe therapy to HMG-CoA reductase inhibitor therapy was also assessed in a double-blind study enrolling 50 patients with homozygous familial hypercholesterolemia. Patients already stabilized on an NCEP Step I or stricter diet and taking open-label atorvastatin 40 mg/day or simvastatin 40 mg/day with or without LDL apheresis were randomized to therapy with atorvastatin or simvastatin 80 mg/day (17 patients), ezetimibe 10 mg/day plus atorvastatin or simvastatin 40 mg/day (16 patients), or ezetimibe 10 mg/day plus atorvastatin or simvastatin 80 mg/day (17 patients) for 12 weeks. The mean percentage change in LDL cholesterol from baseline (on therapy with atorvastatin or simvastatin 40 mg/day) was -7% on an 80 mg statin dose alone compared to -27.5% on ezetimibe plus an 80 mg statin dose. Results for the ezetimibe plus statin 40 mg group were not reported separately, but the overall reduction in LDL cholesterol from baseline in both ezetimibe plus statin groups was -20.7%. Direct LDL cholesterol concentrations fell from a mean of 339 mg/dL at baseline to 319 mg/dL in the statin 80 mg group and from 313 mg/dL at baseline to 247 mg/dL in the ezetimibe plus statin 40 mg or 80 mg group. A reduction in direct LDL levels of 15% or greater occurred in 18% of patients in the statin 80 mg group compared to 58% of patients in the ezetimibe plus statin groups (P=0.001) and 76% in the ezetimibe plus statin 80 mg group (P<0.001).[31,32]

Homozygous Sitosterolemia

Ezetimibe is effective in the treatment of homozygous sitosterolemia. A double-blind, placebo-controlled study enrolled 37 patients with elevated plasma sitosterol levels (greater than 5 mg/dL) on therapy (diet, bile-acid binding resins, HMG-CoA reductase inhibitors, ileal bypass surgery, and/or LDL apheresis). These patients were randomized to receive ezetimibe (30 patients) or placebo (7 patients) therapy for 8-weeks. Ezetimibe reduced plasma sitosterol by 21% from baseline and campesterol by 24% from baseline, while placebo-treated patients had 4% and 3% increases in sitosterol and campesterol, respectively.[1]

Contraindications, Warnings, and Precautions

Ezetimibe is contraindicated in patients with known hypersensitivity to ezetimibe or any of the product ingredients (croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium

lauryl sulfate).[1] Use of ezetimibe in conjunction with an HMG-CoA reductase inhibitor is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.[1]

Ezetimibe use is not recommended in patients with moderate or severe hepatic impairment, since the effects of increased exposure to ezetimibe in such patients is not known.[1]

When used in conjunction with HMG-CoA reductase inhibitors, the contraindications and precautions associated with these agents should be observed (including pregnancy, myopathy, rhabdomyolysis, and monitoring for serum transaminases). Consecutive elevations (three times the upper limit of normal or greater) in serum transaminases occurred in 1.3% of patients treated with ezetimibe plus an HMG-CoA reductase inhibitor compared to 0.4% of patients treated with an HMG-CoA reductase inhibitor alone. The incidence of myopathy or rhabdomyolysis was not increased in patients treated with ezetimibe in conjunction with an HMG-CoA reductase inhibitor.[1]

Ezetimibe is in Pregnancy Category C. In animal studies embryolethal effects were not observed; however, the incidence of some common skeletal findings was increased. Ezetimibe has not been studied in pregnant women, and the agent should be used during pregnancy only if the potential benefit justifies the risk to the fetus.[1]

Ezetimibe is excreted in the milk of lactating rats; exposure to total ezetimibe in nursing pups was up to half that observed in maternal plasma. Ezetimibe should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.[1]

Use in children is not recommended. Limited data are available on the use of ezetimibe in adolescents, including a pharmacokinetic study in which the pharmacokinetics of ezetimibe did not differ from those observed in adults, plus clinical experience in four patients in the sitosterolemia study and five patients in the homozygous familial hypercholesterolemia.[1]

Adverse Reactions

Ezetimibe was well tolerated in the clinical trials. The most common adverse events were similar in nature and incidence to those observed in placebo-treated patients.[5,22] The most commonly observed adverse reactions with monotherapy, regardless of cause, included fatigue, abdominal pain, diarrhea, arthralgia, back pain, infection, and coughing.[1] Table 1 lists the most commonly observed adverse effects in studies evaluating therapy with ezetimibe in comparison with or in conjunction with HMG-CoA reductase inhibitors.[1]

Drug Interactions

Ezetimibe has no effect on the CYP450 enzymes 1A2, 2C8/9, 2D6, 3A4, or N-acetyltransferase, making it unlikely that ezetimibe will cause drug interactions involving CYP450 substrates.[19]

Ezetimibe does not alter the pharmacokinetics of simvastatin, atorvastatin, pravastatin, fluvastatin, or lovastatin.[1,7,30,33-35]

Ezetimibe did not affect the pharmacokinetics or pharmacodynamics of digoxin, glipizide, or warfarin.[1,36,37] The pharmacokinetics of oral contraceptives containing ethinyl estradiol/norgestrel and ethinyl estradiol/

Table 1 Adverse Effects Reported by At Least 2% of the Patients and at an Incidence Greater Than Placebo-Treated in the Ezetimibe Studies[1]

Adverse Effect	Placebo (N=259)	Ezetimibe (N=262)	HMG-CoA Reductase Inhibitors (N=936)	Ezetimibe plus HMG-CoA Reductase Inhibitors (N=925)
Body as a whole				
Chest pain	1.2%	3.4%	2%	1.8%
Dizziness	1.2%	2.7%	1.4%	1.8%
Fatigue	1.9%	1.9%	1.4%	2.8%
Headache	5.4%	8%	7.3%	6.3%
Gastrointestinal				
Abdominal pain	2.3%	2.7%	3.1%	3.5%
Diarrhea	1.5%	3.4%	2.9%	2.8%
Infection				
Pharyngitis	1.9%	3.1%	2.5%	2.3%
Sinusitis	1.9%	4.6%	3.6%	3.5%
Upper respiratory tract infections	10.8%	13%	13.6%	11.8%
Musculoskeletal				
Arthralgia	2.3%	3.8%	4.3%	3.4%
Back pain	3.5%	3.4%	3.7%	4.3%
Myalgia	4.6%	5%	4.1%	4.5%

levonorgestrel were not altered by the concomitant administration of ezetimibe.[1,38]

Cimetidine, glipizide, warfarin, simvastatin, atorvastatin, pravastatin, fluvastatin, and lovastatin did not alter the pharmacokinetics of ezetimibe.[1,7,33-37] Administration of ezetimibe with an antacid reduced the peak concentration of total ezetimibe, but did not affect overall exposure to ezetimibe or total ezetimibe.[39] Administration with cholestyramine decreased the mean AUC of total ezetimibe 55% and that of ezetimibe 80%. Ezetimibe was dosed at least 2 hours before or 4 hours after bile-acid binding resins in some studies in which these agents were administered concurrently.[1] The total ezetimibe level was increased 12-fold in a renal transplant recipient receiving multiple medications including cyclosporine. Close monitoring is recommended for patients receiving concomitant ezetimibe and cyclosporine.[1]

Concomitant ezetimibe and fibrate therapy is not recommended until such use has been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile.[1] Administration with gemfibrozil resulted in a 1.7-fold increase in total ezetimibe bioavailability. Ezetimibe did not affect the bioavailability of gemfibrozil.[1] Administration with fenofibrate resulted in a 64% increase in the ezetimibe peak concentration and a 48% increase in the AUC of total ezetimibe. The pharmacokinetics of fenofibrate were not altered.[1]

Dosing

The recommended dose is 10 mg once daily. Ezetimibe may be taken with or without food.[1] A dose of 10 mg daily was able to sustain trough plasma concentrations above 15 ng/mL, the concentration needed to achieve a 15% reduction in LDL-C.[40] No adjustments in dose are needed for patients with hepatic or renal insufficiency or for elderly patients.[1]

Patients receiving bile acid sequestrant and ezetimibe need to separate the time of administration of these medications. The ezetimibe dose should be given at least 2 hours before or 4 hours after administration of the bile acid sequestrant.[1]

Product Availability

Ezetimibe received FDA approval in November 2002. It is available as 10 mg tablets in bottles of 30, 90, and 500, and unit-dose packages of 100.[1]

Conclusion

Ezetimibe appears to be a safe and modestly effective agent for the reduction of LDL-C. Additional data are necessary to determine its effects on HDL-C and triglycerides. The unique mechanism of action of ezetimibe allows for an additive reduction in LDL-C when administered with an HMG-CoA reductase inhibitor. This may permit the use of lower dosages of the HMG-CoA reductase inhibitors to achieve a similar or greater effect. Additional studies are necessary to determine if the combination of ezetimibe plus a statin is associated with fewer side effects in comparison with increasing the dose of the statin.

References

1. *Zetia* [package literature]. Merck/Schering-Plough Pharmaceuticals; November 2002.
2. Rosenblum SB, et al. Discovery of 1-(4-fluorophenyl)-(3R)-[3-(4-fluorophenyl)-(3S)-hydroxypropyl]-(4S)-(4-hydroxyphenyl)-2-azetidinone (SCH 58235): A designed, potent, orally active inhibitor of cholesterol absorption. *J Med Chem.* 1998;41:973-80.
3. Kramer W, et al. Identification of binding proteins for cholesterol absorption inhibitors as components of the intestinal cholesterol transporter. *FEBS Letters.* 2000; 487:293-7.
4. Sudhop T, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation.* 2002;106:1943-8.
5. Bays HE, et al. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: Pooled analysis of two phase II studies. *Clin Ther.* 2001;23:1209-30.
6. Dujovne CA, et al. Ezetimibe, a selective cholesterol absorption inhibitor, improves plasma lipids in hypercholesterolemic patients [abstract]. *Circulation.* 2001;104(17, suppl):851.
7. Kosoglou T, et al. Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor ezetimibe and atorvastatin [abstract]. *J Am Coll Cardiol.* 2001;37 (2, suppl A):229A.
8. Kosoglou T, et al. Pharmacodynamic interaction between cerivastatin and the selective cholesterol absorption inhibitor ezetimibe [abstract]. *Eur Heart J.* 2001;22(suppl):252.
9. Dujovne C, et al. Does cholesterol and/or fat intake affect plasma lipid efficacy of ezetimibe [abstract]? *J Am Coll Cardiol.* 2002;39(5, suppl 1):227A.
10. van Heek M, et al. Ezetimibe selectively inhibits intestinal cholesterol absorption in rodents in the presence and absence of exocrine pancreatic function. *Br J Pharmacol.* 2001;134:409-17.
11. van Heek M, et al. Ezetimibe, a potent cholesterol absorption inhibitor, normalizes combined dyslipidemia in obese hyperinsulinemic hamsters. *Diabetes.* 2001;50:1330-5.
12. Davis HR Jr, et al. Ezetimibe, a potent cholesterol absorption inhibitor, inhibits the development of atherosclerosis in ApoE knockout mice. *Arterioscler Thromb Vasc Biol.* 2001;21:2032-8.
13. Davis HR Jr, et al. The synergistic hypocholesterolemic activity of the potent cholesterol absorption inhibitor, ezetimibe, in combination with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in dogs. *Metabolism.* 2001;50:1234-41.
14. van Heek M, et al. Comparison of the activity and disposition of the novel cholesterol absorption inhibitor, SCH58235, and its glucuronide, SCH60663. *Br J Pharmacol.* 2000;129:1748-54.
15. Patrick JE, et al. Disposition of the selective cholesterol absorption inhibitor ezetimibe in healthy male subjects. *Drug Metab Dispos.* 2002;30:430-7.
16. Reyderman L, et al. Dose-proportionality of ezetimibe [abstract]. *Clin Pharmacol Ther.* 2002;71(2):P97.
17. Ezzet F, et al. A population pharmacokinetic model that describes multiple peaks due to enterohepatic recirculation of ezetimibe. *Clin Ther.* 2001;23:871-85.

18. Courtney RD, et al. Effect of food on the oral bioavailability of ezetimibe [abstract]. *Clin Pharmacol Ther.* 2002;71(2):P80.

19. Zhu Y, et al. Effect of SCH 58235 on the activity of drug metabolizing enzymes *in vivo* [abstract]. *Clin Pharmacol Ther.* 2000;67(2, suppl):PIII-43.

20. Kosoglou T, et al. Multiple-dose safety and pharmacokinetics of ezetimibe in adolescent children [abstract]. *Clin Pharmacol Ther.* 2001;69(2, suppl):P52.

21. Reyderman L, et al. Pharmacokinetics of ezetimibe in subjects with normal renal function or severe chronic renal insufficiency [abstract]. *Clin Pharmacol Ther.* 2002;71(2):P27.

22. Lipka LJ, et al. Ezetimibe significantly lowers low-density lipoprotein cholesterol in subjects with primary hypercholesterolaemia [abstract]. *Eur Heart J.* 2001;22(suppl):252.

23. Dujovne CA, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am J Cardiol.* 2002;90:1092-7.

24. Stein E. Results of phase I/II clinical trials with ezetimibe, a novel selective cholesterol absorption inhibitor. *Eur Heart J.* 2001;3(suppl E):E11-16.

25. Gagne C, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol.* 2002;90:1084-91.

26. Bays H, et al. Ezetimibe added to ongoing statin therapy for treatment of primary hypercholesterolemia [abstract]. *J Am Coll Cardiol.* 2002;39(5, suppl 1):228A.

27. Melani L, et al. Review of the consistency of effect of ezetimibe co-administered with statins in patients with primary hypercholesterolemia with or without hypertriglyceridemia [abstract]. *Diabetes.* 2002;51(suppl 2):529-P.

28. Davidson M, et al. Ezetimibe co-administered with simvastatin in 668 patients with primary hypercholesterolemia [abstract]. *J Am Coll Cardiol.* 2002;39(5, suppl 1):226A-227A.

29. Ballantyne C, et al. Ezetimibe co-administered with atorvastatin in 628 patients with primary hypercholesterolemia [abstract]. *J Am Coll Cardiol.* 2002;39(5, suppl 1):227A.

30. Kosoglou T, et al. Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor ezetimibe and simvastatin. *Br J Clin Pharmacol.* 2002;54:309-19.

31. Gagne C, et al. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation.* 2002;105:2469-75.

32. Gagne C, et al. Ezetimibe significant reduced low-density lipoprotein cholesterol in homozygous familial hypercholesterolemia [abstract]. *J Am Coll Cardiol.* 2002;39(5, suppl 1):227A.

33. Statkevich P, et al. SCH 58235 does not affect the pharmacokinetics of simvastatin [abstract]. *Clin Pharmacol Ther.* 2000;67(2, suppl):PIII-16.

34. Zhu Y, et al. Lack of a pharmacokinetic interaction between ezetimibe and atorvastatin [abstract]. *Clin Pharmacol Ther.* 2001;69(2, suppl):P68.

35. Reyderman L, et al. No pharmacokinetic drug interaction between ezetimibe and lovastatin [abstract]. *Clin Pharmacol Ther.* 2001;69(2, suppl):P66.

36. Statkevich P, et al. Ezetimibe does not affect the pharmacokinetics and pharmacodynamics of glipizide [abstract]. *Clin Pharmacol Ther.* 2001;69(2, suppl):P67.

37. Bauer KS, et al. Ezetimibe does not affect the pharmacokinetics or pharmacodynamics of warfarin [abstract]. *Clin Pharmacol Ther.* 2001;69(2, suppl):P5.

38. Keung ACF, et al. Ezetimibe does not affect the pharmacokinetics of oral contraceptives [abstract]. *Clin Pharmacol Ther.* 2001;69(2, suppl):P55.

39. Courtney RD, et al. Effect of antacid on the pharmacokinetics of ezetimibe [abstract]. *Clin Pharmacol Ther.* 2002;71(2):P80.

40. Ezzet F, et al. The plasma concentration and LDL-C relationship in patients receiving ezetimibe. *J Clin Pharmacol.* 2001;41:943-9.

Cada D (Ed), Baker D, Levien T. Ezetimibe (Zetia), *The Formulary Monograph Service*, Facts and Comparisons, March, 2003.

Selected FDA Safety Alerts

Avonex (Interferon beta-1a)

Audience: Neurologists and other healthcare professionals

Biogen and FDA revised the WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, PATIENT INFORMATION, and CLINICAL STUDIES sections of the prescribing information to include important new safety information and a patient Medication Guide. Updated safety information includes a cautionary note regarding use in patients with depression and other severe psychiatric symptoms.

Post-marketing reports of depression, suicidal ideation and/or development of new or worsening of pre-existing psychiatric disorders, including psychosis, and reports of anaphylaxis, pancytopenia, thrombocytopenia, autoimmune disorders of multiple target organs, and hepatic injury manifesting itself as elevated serum enzyme levels and hepatitis were added to the labeling.

An FDA-approved Patient Medication Guide, providing important patient safety information and comprehensive instructions for patient self-administration of Avonex, was added.

Lindane (gamma-hexachlorocyclohexane)

Audience: Primary Care providers, Pharmacists, and consumers

FDA issued a Public Health Advisory concerning the use of topical formulations of Lindane Lotion and Lindane Shampoo for the treatment of scabies and lice. A boxed warning emphasizes that it is a second-line treatment, updates information about its potential risks, especially in children and adults weighing less than 110 pounds, and reminds practitioners that reapplication of Lindane Lotion or Lindane Shampoo is not the appropriate treatment, if itching continues after the single treatment.

A Medication Guide, designed to inform patients of the risks of Lindane products and provide instructions for appropriate use of the drugs, must now be dispensed by the pharmacist with each new prescription.

Permax (pergolide mesylate)

Audience: Neurologists and other healthcare professionals

Lilly and FDA revised the WARNINGS section of the prescribing information to inform healthcare professionals of reports of cardiac valvulopathy involving one or more valves in patients receiving Permax therapy.

Prempro/Premphase (conjugated estrogens/ medroxyprogesterone acetate tablets)
Premarin (conjugated estrogens tablets, USP)

Audience: Reproductive healthcare professionals

FDA and Wyeth revised the prescribing information to include a boxed warning, which states that estrogens and estrogens plus progestin therapies should not be used for the prevention of cardiovascular disease.

The boxed warning includes risk information from the Women's Health Initiative (WHI) study. The study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Procrit (epoetin alfa)

Audience: Pharmacists and Oncological healthcare professionals

FDA and Ortho Biotech Products alerted healthcare providers and consumers about the existence of three lots of counterfeit product labeled as Procrit (epoetin alfa):

The counterfeit Procrit has been found to be contaminated with bacteria and therefore represents a significant potential hazard to consumers. FDA testing has demonstrated that some counterfeit product contains no active ingredient.

Rapamune (sirolimus)

Audience: Transplantation surgeons and other healthcare professionals

Wyeth, in cooperation with FDA, notified healthcare professionals of post-marketing reports of bronchial anastomotic dehiscence, including fatal cases, in lung transplant patients treated with Rapamune in combination with tacrolimus and corticosteroids. The safety and efficacy of Rapamune as immunosuppressive therapy has not been established in lung transplant patients.

Serevent (salmeterol xinafoate)

Audience: Pulmonary specialists and other healthcare professionals

GlaxoSmithKline notified healthcare professionals of important new safety information on use of Serevent in patients with asthma. Recent findings from an interim analysis of a large Serevent safety study have prompted further review of the potential association between Serevent and rare, but potentially serious, respiratory adverse events.

Serzone (nefazodone HCl)

Audience: Neuropsychiatric healthcare professionals and Pharmacists

Bristol-Myers Squibb notified healthcare professionals of medication errors due to name confusion between Serzone, indicated for the treatment of depression, and Seroquel, a product of AstraZeneca, indicated for the treatment of schizophrenia. The overlapping strengths (100 mg and 200 mg), the dosage form (tablets), the dosing interval (BID), and the fact that these two products are stocked close together in pharmacies were critical in causing these medication errors.

Note: **Detailed information on these and other FDA safety alerts is available via the FDA homepage (*www.fda.gov*).**

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- Pegylated Interferon Alfa-2a (Pegasys), an injectable immunomodulator for the treatment of chronic hepatitis C
- Adefovir (Hepsera), an oral acyclic nucleotide analog for the treatment of chronic hepatitis B
- Citalopram (Celexa), an oral selective serotonin reuptake inhibitor for the treatment of depression
- Polysaccharide-iron complex (Niferex), an oral iron supplement
- Testosterone (Androgel), a topical testosterone gel

Deletions

- Triamcinolone cream, 0.5%
- Tretinoin cream, 0.025% and 0.05%
- Procyclidine (Kemadrin) tablets
- Maprotiline (Ludiomil) tablets

FDA Safety Alerts

- You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.

- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov.* In the message body enter: *subscribe medwatch* and your e-mail address.

Drug Information Service

- Patient-specific pharmacotherapy evaluation and management
- Comprehensive information about medications, biologics, and nutrients
- Critical evaluation of drug therapy literature
- Assistance with study design and protocol development
- Clinical trial drug safety monitoring
- Investigational drug information
- Parenteral nutrition assessment and management

301-496-2407
Pager 301-285-4661
Building 10, Room 1S-259